DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

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Docket No. 2007N- 0311

Dear Midodrine Application Holder:

As you know, midodrine hydrochloride was approved under the Food and Drug Administration's (FDA's) accelerated approval regulations in 21 CFR part 314, subpart H. The approval of midodrine hydrochloride was based on a surrogate endpoint and completion of phase 4 studies verifying clinical benefit was a condition of approval (see § 314.510; approval letter enclosed). To date, the holder of the midodrine hydrochloride new drug application (NDA) has failed to obtain approval for the required phase 4 studies verifying clinical benefit. If those studies are not approved in a timely manner, that NDA (and all ANDAs referencing that NDA) will be subject to withdrawal under the withdrawal provisions of subpart H (§ 314.530). As a result, several holders of approved abbreviated applications for midodrine hydrochloride have considered whether to conduct the requisite studies and have requested FDA advice regarding the availability and potential scope of 3-year new clinical studies exclusivity if holders of approved midodrine applications were to collaboratively or individually complete the required post-marketing studies to verify clinical benefit for midodrine hydrochloride. Because these proposals raise issues of first impression and will affect more than one midodrine application holder, we are seeking your input on a number of related legal/regulatory questions before responding. Please consider commenting on the following:

1) If the post-marketing studies have been previously required as a condition of continued approval of midodrine hydrochloride under subpart H and one or more ANDA applicants complete those studies, are those studies eligible for 3-year exclusivity? Under what theory?
2) Does the answer to #1 depend on whether the studies merely validate the use of the surrogate endpoint or change the indication or other condition of use for the approved drug product?
3) Does the same result apply if the sponsor of the NDA, itself, completes phase 4 studies that were required as a condition of approval under subpart H. Why or why not?
4) If 3-year exclusivity is available for the required phase 4 studies and holders of approved ANDAs collaborate to conduct those studies, is there legal authority to permit them to share 3-year exclusivity? If not, can the first applicant to obtain approval of its supplement selectively waive its 3-year exclusivity in favor of the other collaborators on the studies?
5) Under the statute and applicable regulations, could a study be "conducted or sponsored by the applicant" as required for 3-year exclusivity if that applicant paid less than 50 percent of the costs of the study? Why or why not?
6) If studies are completed and certain holders of approved ANDAs or the NDA holder does not collaborate, does FDA have authority under section 505(e) of the Federal Food, Drug, and Cosmetic Act to withdraw approval of those applications? Does FDA have such authority under any other statutory or regulatory provision? Would notice and opportunity for hearing be required before withdrawal?

2007N-0311
FDA-2007-N-0475

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To ensure a more complete and public discussion, FDA will make these questions and any responses received available in a public docket at Docket No. 2007N-0311. Please send your responses, if any, by September 7, 2007, to:

Food and Drug Administration
Division of Dockets Management
5630 Fishers Lane, HFA- 305, Room 1061
Rockville, Maryland 20852

We remind you that exclusivity determinations are generally made by FDA after approval of an application or supplement, based on our findings and the specific labeling changes approved. Exclusivity issues should not delay any efforts to undertake the needed phase 4 studies to show clinical benefit for midodrine. Thank you in advance for your input.

Sincerely,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Norman L. Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: September 6, 1996 Approval Letter for NDA 19-815

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-815

SEP 6 1996

Robbins Pharmaceutical Corporation
Attention: Mr. Drew Karian
Meridian Center II
Four Industrial Way West
Eatontown, NJ 07724-2274

Dear Mr. Karian:

Please refer to your April 26, 1988 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ProAmatine (midodrine HCl) 2.5 and 5 mg Tablets.

We acknowledge receipt of your amendments and correspondence dated June 10, 14, 19 and 26, July 5, 8 and 15 and August 6, 13, 15 and 23 (two), 1996.

The new drug application provides for the use of ProAmatine for the treatment of symptomatic orthostatic hypotension (OH). The indication is based on ProAmatine's effect on increases in 1-minute standing systolic blood pressure, a surrogate marker considered likely to correspond to a clinical benefit. At present, clinical benefits of ProAmatine, principally improved ability to perform life activities, have not been established.

We have completed the review of this application including the submitted draft labeling, according to the regulations for accelerated approval, and have concluded that adequate information has been presented to approve ProAmatine (midodrine HCl) 2.5 and 5 mg Tablets for use as recommended in the enclosed marked-up draft. Accordingly, the application is approved under 21 CFR 314.520. Approval is effective on the date of this letter. Marketing of this drug product and related activities are to be in accordance with the substance and procedures of the referenced accelerated approval regulations. In particular, we remind you that all promotional materials must be submitted at least 30 days prior to the intended time of initial dissemination of the labeling or the initial publication of the advertisement. Please submit one copy to NDA 19-815 and a second copy directly to the Division of Drug Marketing, Advertising, and Communications. Such submissions should be prominently labeled "Accelerated Approval Materials."

We remind you of your Phase 4 commitments specified in your submissions dated May 20 and August 15, 1996. These commitments, along with any completion dates agreed upon, are listed below.

As described under 21 CFR 314.570, approval under this section requires that you study the drug further to verify and describe its clinical benefit. The studies required to confirm the clinical benefit of midodrine were discussed at the July 18, 1996 meeting with the Agency. Draft protocols for the Phase 4 trials provided in your August 15, 1996 submission are currently under review. Our recommendations for the proposed studies will be provided under separate cover. Upon receipt of these

recommendations, the studies should be carried out with due diligence. The projected time for completion of these trials was estimated, at the July 18 meeting, to be 3 to 4 years, depending on rate of enrollment.

Protocols, data, and final reports should be submitted to your IND for this product with a copy of the cover letter submitted to this NDA. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

If these studies do not provide verification of clinical benefit to conclude that the drug is safe and effective for an intended use, you will comply with the accelerated approval withdrawal procedures described in 21 CFR 314.530. Additional studies, including treatment IND protocols, could proceed after such a withdrawal if the data supported continued trials.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 19-815. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/
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Gary Buehler
8/7/2007 12:57:31 PM

Norman Stockbridge
8/7/2007 04:53:45 PM